Supplemental Data:

Table 1. Geometry change from reactant to TS in the proton transfer reaction of YH_2(DOTA).

	(a) YH_2(DOTA)		(b) YH(DOTA)	
	Reactant	TS	Reactant	TS
r(O-Y) (Å)	2.14	2.14	2.18	2.17
	2.17	2.30, 2.51	2.20	2.20
	2.19	2.18	2.18	2.18
	2.20	2.31	2.27	2.38
r(H-Y) (Å)	3.12	3.06	2.93	2.72
	3.17	3.28		
r(N-Y) (Å)	4.01	3.94	2.75	2.65
r(N-H) (Å)	1.01, 1.01	1.33, 1.01	1.02	1.26
r(H···O) (Å)	2.16, 2.23	1.15, 2.34	1.81	1.18

Table 2. Detailed energetics (kcal/mol) involved in deprotonation of YH_2(DOTA).

(a) YH_2(DOTA)	$E^{\dagger}$(N-to-O proton transfer)	ΔE(4-coord to 3-coordinate)
Gas-phase	1.2	36.8
Solvation energy	21.2	-20.3
Aqueous phase	**22.4**	**16.6**
(b) YH(DOTA)		
Gas-phase	2.0	22.1
Solvation energy	10.1	-0.5
Aqueous phase	**12.1**	**21.6**

Table 3. Acid Dissociation Constants and Titration Shifts for DO4Pr in 0.1 M KCl at 25°C.

	Titration shifts (ppm)[b]			pK_as			Microscopic	DOTA[c]
Protons[a]	1	2	3	1	2	3	pK_as	pK_as
G Carboxylates	0.155	0.023	0.060	3.35	3.88	3.50	3.22[d]	1.24
							3.74[d]	1.84
F Carboxylates	0.113	--	--	4.44	--	--	4.28[d]	4.27
							4.80[d]	4.87
G Amines	0.104	0.213	0.318	9.59	9.68	9.59	9.62 (±0.04)	9.66
	0.068	0.255	0.078	11.86	12.01	11.90	11.92 (±0.06)	10.86

a.) Labeled as in Keire and Kobayashi, 1999.

b.) The titration shifts were calculated from the chemical shift values obtained in the pKa fits (δ_{HA}-δ_A).

c.) Solution conditions 0.1 M KCl and 25°C, Keire and Kobayashi, 1999

d.) These values are calculated microscopic acid dissociation constants derived from the relationship between macroscopic and microscopic pK_as (see Edsall and Wyman 1958). The mean of the three measured G carboxylate values {3.58 (±0.22)} was used for the calculation of the microscopic G carboxylate pK_as.

Table 4. Selected Acid Dissociation Constants and Titration Shifts for DO3A1Pr in 0.1 M KCl at 25°C.

	Titration shifts (ppm)[b]				pK_as				Microscopic
Protons[a]	E1	E2	F	G	E1	E2	F	G	pK_as
G Carboxylate	--	--	--	0.524	--	--	--	2.20	2.20
E Carboxylate	0.344	0.274	-0.173	--	2.79	3.06	2.79	--	2.88(±0.13)
F Carboxylates	-0.090	0.093	0.209	--	4.39	4.40	4.32	--	4.00[c]
									4.68[c]
E Amine	0.225	0.147	0.167	0.236	10.44	10.60	10.60	10.23	9.87[d]
G Amine									11.07[d]

a.) Labeled as in Figure 1.

b.) The titration shifts were calculated from the chemical shift values obtained in the pKa fits (δ_{HA}-δ_A).

c.) These values are calculated microscopic acid dissociation constants derived from the relationship between macroscopic and microscopic pK_as (see Edsall and Wyman 1958). The mean of the three measured macroscopic F carboxylate values {4.37(±0.04)} was used for the calculation of the microscopic F carboxylate pK_as.

d.) The mean of the four measured macroscopic G and E amine values {10.47 (±0.15)} was used for the calculation of the microscopic G and E amine pK_as.

Supplemental Figure legends:

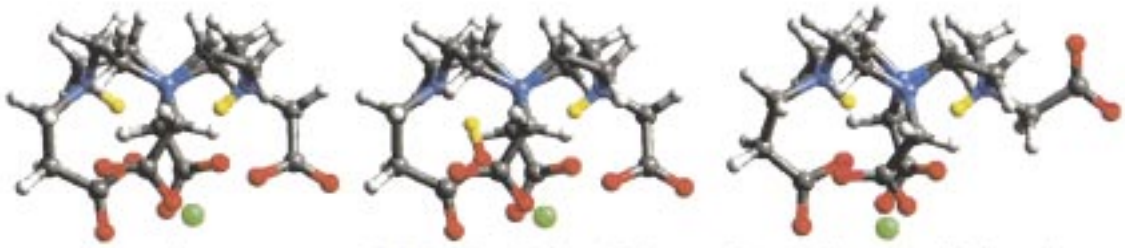
Figure 1. Two ways of deprotonation from $YH_2(DO3A1Pr)_{prac}$ (**IIa**).

Figure 2. The 2.3 to 4.1 ppm region of the 500 MHz ^{1}H-NMR spectra of 1 mM DO3A1Pr in 90% H_2O/10% D_2O at pH 1.) 2.0, 2.) 2.9, 3.) 3.6, 4.) 5.0, 5.) 9.8, and 6.) 10.2. Signals from the various DO3A1Pr protons are labeled in the accompanying structure and the spectra. The signals marked with an asterisk in the spectra are from protons on a hydroxy-proionic acid impurity.

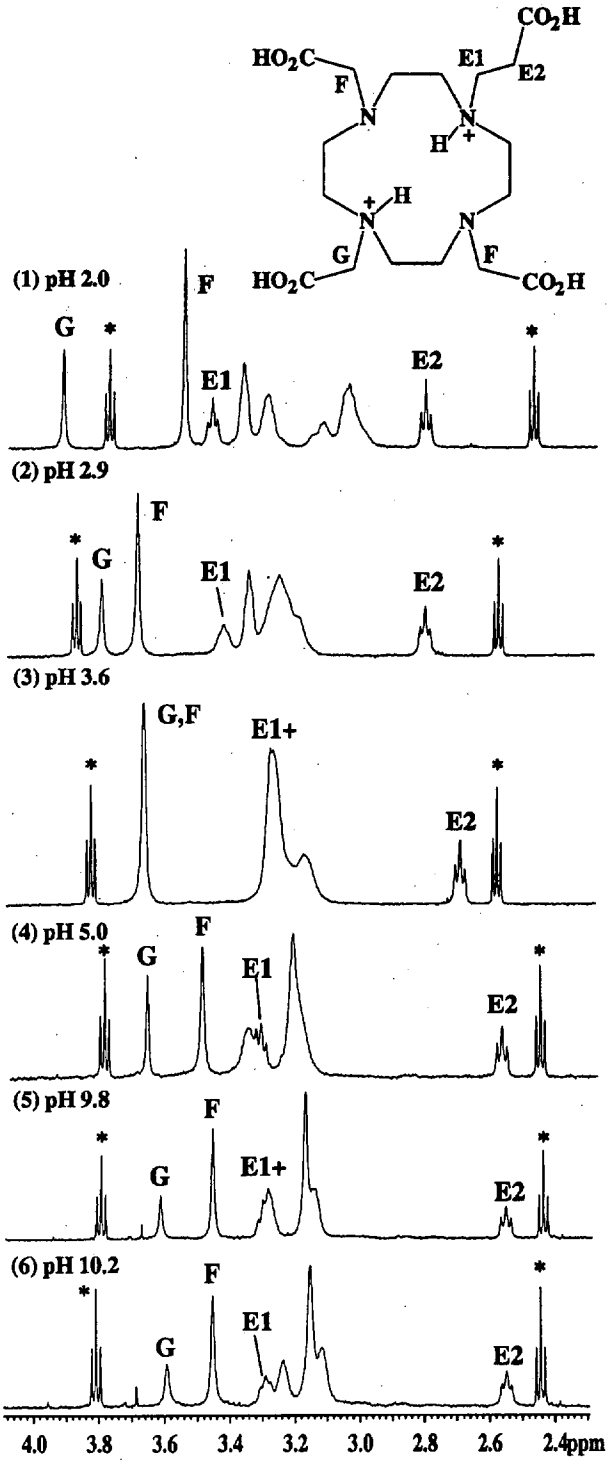
Figure 3. Two pathways to deprotonation of YH(DOTA) (i.e. proton exposure to outside base in solvent phase) (a) N-to-O proton transfer; proton (yellow) transfer from ring nitrogen (blue) to carboxylate oxygen (red) of YH(DOTA) (Yttrium in green): (left) reactant, (middle) transition state, and (right) product and (b) cage-opening (same color scheme).

Supplemental Figures.

Supplemental Figure 1.



4-coordinate TS (NH to HO on Pr) 3-coordinate (with Ac up)


CO2H
HO2C
E1
E2
F
N
N
H+
+H
N
N
G
F
HO2C
CO2H
(1) pH 2.0
F
G
*
E1
E2
*
(2) pH 2.9
F
*
G
E1
E2
*
(3) pH 3.6
G,F
E1+
*
E2
*
(4) pH 5.0
F
*
G
E1
E2
*
(5) pH 9.8
F
*
G
E1+
E2
*
(6) pH 10.2
F
*
G
E1
E2
*
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4ppm

Supplemental Figure 3.

(a)

(b)